HAVRIX 1440 and HAVRIX JUNIOR

SCHEDULING STATUS:

S4

PROPRIETARY NAME AND DOSAGE FORM:

HAVRIX 1440 Suspension for injection

HAVRIX JUNIOR Suspension for injection

COMPOSITION:

HAVRIX, hepatitis A virus vaccine is a sterile suspension containing formaldehyde-inactivated hepatitis A virus (HM175 hepatitis A virus strain) adsorbed onto aluminium hydroxide.

HAVRIX 1440:

One dose (1,0 ml) of HAVRIX 1440 contains:

Hepatitis A virus (inactivated)[1,2]	1440 ELISA Units
[1]Produced on human diploid (MRC-5) cells	
[2]Adsorbed on aluminium hydroxide, hydrated	0,50 mg Al^{3+}

HAVRIX JUNIOR:

One dose (0,5 ml) of HAVRIX JUNIOR contains:

Hepatitis A virus (inactivated)[1,2]	720 ELISA Units
[1]Produced on human diploid (MRC-5) cells	
[2]Adsorbed on aluminium hydroxide, hydrated	0,25 mg Al^{3+}

Excipients: Amino acids for injections, disodium phosphate, monopotassium phosphate, polysorbate 20, potassium chloride, sodium chloride, water for injections.

Residues: Neomycin sulphate (HAVRIX JUNIOR: less than 10 ng and HAVRIX 1440: less than 20 ng).

PHARMACOLOGICAL CLASSIFICATION:

A 30.2 Antigens

PHARMACOLOGICAL ACTION:

Pharmacodynamic properties:

HAVRIX confers immunity against hepatitis A virus (HAV) infection by inducing the production of specific anti-HAV antibodies.

Long-term persistence of serum antibodies to hepatitis A virus after vaccination with HAVRIX is under evaluation.

Data available after 17 years allows prediction that at least 95 % and 90 % of subjects will remain seropositive (> 15 mIU/ml) 30 and 40 years after vaccination, respectively (see Table 1).

Table 1: Predicted proportion with anti-HAV level ≥ 15 mIU/ml and 95 % confidence intervals for studies HAV-112 and HAV-123.

Year	≥ 15 mIU/ml	95 % CI	
		LL	UL
Predictions for HAV-112			
25	97,69 %	94,22 %	100 %
30	96,53 %	92,49 %	99,42 %
35	94,22 %	89,02 %	98,93 %
40	92,49 %	86,11 %	97,84 %
Predictions for HAV-123			
25	97,22 %	93,52 %	100 %
30	95,37 %	88,89 %	99,07 %
35	92,59 %	86,09 %	97,22 %

40	90,74 %	82,38 %	95,37 %

Current data do not support the need for further booster vaccination among immunocompetent subjects after a 2 dose vaccination course.

Impact of mass vaccination on disease incidence:

A reduction in the incidence of hepatitis A was observed in countries where a two-dose HAVRIX immunisation programme was implemented for children in their second year of life:

- In Israel, two retrospective database studies showed 88 % and 95 % reduction in hepatitis A incidence in the general population 5 and 8 years after the implementation of the vaccination program, respectively. Data from National Surveillance also showed a 95 % reduction in hepatitis A incidence as compared to the pre-vaccination era.
- In Panama, a retrospective database study showed a 90 % reduction in reported hepatitis A incidence in the vaccinated population, and 87 % in the general population, 3 years after implementation of the vaccination programme. In paediatric hospitals in Panama City, confirmed acute hepatitis A cases were no longer diagnosed 4 years after implementation of the vaccination programme.
- The observed reductions in hepatitis A incidence in the general population (vaccinated and non-vaccinated) in both countries demonstrate herd immunity.

Pharmacokinetic properties:

Evaluation of pharmacokinetic properties is not required for vaccines**.**

INDICATIONS:

HAVRIX is indicated for active immunisation against hepatitis A virus (HAV) infection in subjects at risk of exposure to HAV.

HAVRIX will not prevent hepatitis infection caused by other agents such as hepatitis B virus, hepatitis C virus, hepatitis E virus or other pathogens known to infect the liver.

In areas of low and intermediate prevalence of hepatitis A, immunisation with HAVRIX is particularly recommended in subjects who are, or will be, at increased risk of infection such as:

Travellers: Persons moving from areas of low endemicity to areas of high endemicity.

Armed forces: Armed Forces personnel who travel to higher endemicity areas or to areas where hygiene is poor, have an increased risk of HAV infection. Active immunisation is indicated for these individuals.

Persons for whom hepatitis A is an occupational hazard or for whom there is an increased risk of transmission.

Persons at increased risk due to their sexual behaviour. Homosexuals, persons with multiple sexual partners.

Haemophiliacs.

Abusers of injectable drugs.

Contacts of infected persons.

Persons who require protection as part of hepatitis A outbreak control or because of regionally elevated morbidity.

Specific population groups known to have a higher incidence of hepatitis A.

Subjects with chronic liver disease or who are at risk of developing chronic liver disease (e.g. hepatitis B and hepatitis C carriers and alcohol abusers). Hepatitis A tends to compromise the outcome of the chronic liver disease.

In areas of **intermediate to high prevalence** of hepatitis A, susceptible individuals may be considered for active immunisation. These include children and adolescents especially in high socio-economic groups and urban areas.

CONTRA-INDICATIONS:

HAVRIX should not be administered to subjects with known hypersensitivity to any components of the vaccine, or to subjects having shown signs of hypersensitivity after previous HAVRIX administration.

WARNINGS AND SPECIAL PRECAUTIONS:

Do not freeze; discard if vaccine has been frozen.

The administration of HAVRIX should be postponed in subjects suffering from acute severe febrile illness. The presence of a minor infection, however, is not a contra-indication.

It is possible that subjects may be in the incubation period of a hepatitis A infection at the time of immunisation. It is not known whether HAVRIX will prevent hepatitis A in such cases.

In haemodialysis patients and in subjects with an impaired immune system adequate anti-HAV antibody titres may not be obtained after the primary immunisation course and such patients may therefore require administration of additional doses of vaccine. It is not known whether HAVRIX will prevent hepatitis A in such cases and it is advised that antibody titres be done in these cases to monitor the effectiveness.

Syncope (fainting) can occur following, or even before, any vaccination as a psychogenic response to the needle injection. It is important that procedures are in place to avoid injury from faints.

HAVRIX can be given to HIV-infected persons.

Seropositivity against Hepatitis A is not a contra-indication.

Appropriate medication (e.g. adrenaline) should be readily available for immediate use in case of anaphylaxis or anaphylactoid reactions following the administration of the vaccine. For this reason, the vaccinee should remain under medical supervision for 30 minutes after immunisation.

HAVRIX should be administered with caution to subjects with thrombocytopenia or a bleeding disorder, since bleeding may occur following an intramuscular administration to these subjects. Firm pressure should be applied to the injection site (without rubbing) for at least 2 minutes.

INTERACTIONS:

Since HAVRIX is an inactivated vaccine its concomitant use with other inactivated vaccines is unlikely to result in interference with the immune responses.

HAVRIX can be given concomitantly with any of the following vaccines: typhoid, yellow fever, cholera (injectable), tetanus, or with monovalent and combination vaccines comprised of measles, mumps, rubella and varicella.

Concomitant administration of immunoglobulins does not impact the protective effect of the vaccine.

When concomitant administration of other vaccines or of immunoglobulins is considered necessary, the vaccines must be given with different syringes and at different injection sites.

HAVRIX must not be mixed with other vaccines or immunoglobulins in the same syringe.

Early clinical experiences on the concomitant administration of HAVRIX and the recombinant hepatitis B virus vaccine have been satisfactory. No interference in the respective immune responses to both antigens has been observed.

PREGNANCY AND LACTATION:

Pregnancy: The effect of HAVRIX on fetal development has not been assessed. HAVRIX should be used during pregnancy, only when clearly needed.

Lactation: Adequate human data on use during lactation and adequate animal reproduction studies are not available. HAVRIX should be used during lactation, only when clearly needed.

DOSAGE AND DIRECTIONS FOR USE:

HAVRIX 1440 (1440 ELISA UNITS):

Each dose consists of a 1,0 ml sterile suspension.

Adults and children 16 years of age and older:

A single dose (1,0 ml suspension) of HAVRIX 1440 (1440 ELISA Units) is used for primary immunisation.

HAVRIX JUNIOR (720 ELISA UNITS):

Children and adolescents from 1 year up to and including 15 years of age:

A single dose (0,5 ml suspension) of HAVRIX JUNIOR (720 ELISA Units) is used for primary immunisation.

Booster vaccination: A booster dose is recommended at any time between 6 and 12 months after the primary dose of HAVRIX 1440 (1440 ELISA Units) or HAVRIX JUNIOR (720 ELISA Units) in order to ensure long term antibody titres.

Route of administration: HAVRIX is for **intramuscular** administration. The vaccine should be injected in the deltoid region in adults and children and in the antero-lateral part of the thigh in young children.

The vaccine should not be administered in the gluteal region or subcutaneously/intradermally since administration by these routes may result in a less than optimal anti-HAV antibody response.

The vaccine should never be administered intravenously.

Use and Handling: HAVRIX should be inspected visually for any particulate matter or discolouration prior to administration. Before use of HAVRIX, the vial/syringe should be well shaken to obtain a slightly opaque white suspension. Discard if the contents of the vial/syringe appear otherwise.

SIDE EFFECTS:

The safety profile presented below is based on data from more than 5 300 subjects.

Frequencies per dose are defined as follows:

Very common: ≥ 1/10

Common: ≥ 1/100, < 1/10

Uncommon: ≥ 1/1 000, < 1/100

Rare: ≥ 1/10 000, < 1/1000

Very rare: < 1/10 000, including isolated reports

- **Clinical Trial Data:**

  Infections and infestations:

  Uncommon: upper respiratory tract infection, rhinitis

  Metabolism and nutrition disorders:

  Common: appetite lost

  Psychiatric disorders:

  Very common: irritability

  Nervous system disorders:

  Very common: headache

  Common: drowsiness

  Uncommon: dizziness

  Rare: hypoaesthesia, paraesthesia

  Gastrointestinal disorders:

  Common: gastrointestinal symptoms (such as diarrhoea, nausea, vomiting)

  Skin and subcutaneous tissue disorders:

  Uncommon: rash

  Rare: pruritus

Musculoskeletal and connective tissue disorders:

Uncommon: myalgia, musculoskeletal stiffness

General disorders and administration site conditions:

Very common: pain and redness at the injection site, fatigue

Common: malaise, fever (≥ 37,5 °C), injection site reaction (such as swelling or induration)

Uncommon: influenza like illness

Rare: chills.

- **Post-marketing Surveillance:**

  Immune system disorders: anaphylaxis, allergic reactions including anaphylactoid reactions and mimicking serum sickness

  Nervous system disorders: convulsions

  Vascular disorders: vasculitis

  Skin and subcutaneous tissue disorders: angioneurotic oedema, urticaria, erythema multiforme

  Musculoskeletal and connective tissue disorders: arthralgia.

KNOWN SYMPTOMS OF OVERDOSAGE AND PARTICULARS OF ITS TREATMENT:

Cases of overdose have been reported during post-marketing surveillance. Adverse events reported following overdosage were similar to those reported with normal vaccine administration.

IDENTIFICATION:

Turbid liquid, with a slow settling white deposit. The supernatant is colourless. The precipitate is easily brought into suspension when shaken.

PRESENTATION:

HAVRIX 1440:

Presented in a clear glass vial or pre-filled glass syringe.

Vials are available in packs of 1 and 10, or blisters of 25. Pre-filled syringes are available in packs of 1 or 5.

HAVRIX JUNIOR:

Presented in a glass vial or a pre-filled glass syringe (with or without fixed needle).

STORAGE INSTRUCTIONS:

HAVRIX must be stored at +2 °C to +8 °C.

DO NOT FREEZE; discard if vaccine has been frozen.

Shake well before use.

Keep out of reach of children.

Protect from light.

REGISTRATION NUMBER:

HAVRIX 1440: 29/30.1/0310

HAVRIX JUNIOR: 31/30.1/0294

NAME AND BUSINESS ADDRESS OF THE HOLDER OF THE CERTIFICATE OF REGISTRATION:

GlaxoSmithKline South Africa (Pty) Ltd

39 Hawkins Avenue

Epping Industria 1, 7460

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MANUFACTURER:

GlaxoSmithKline Biologicals S.A.

Rue de L'Institut , 89

1330 Rixensart, Belgium

Botswana:
Havrix 1440: Reg No BOT9800202 S2
Havrix Junior: Reg No BOT9800201 S2

Namibia:
Havrix 1440: Reg No 04/30.1/0883 NS1
Havrix Junior: Reg No 04/30.1/0884 NS1

Malawi:
Havrix 1440: Reg No PMPB/PL270/113 POM

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